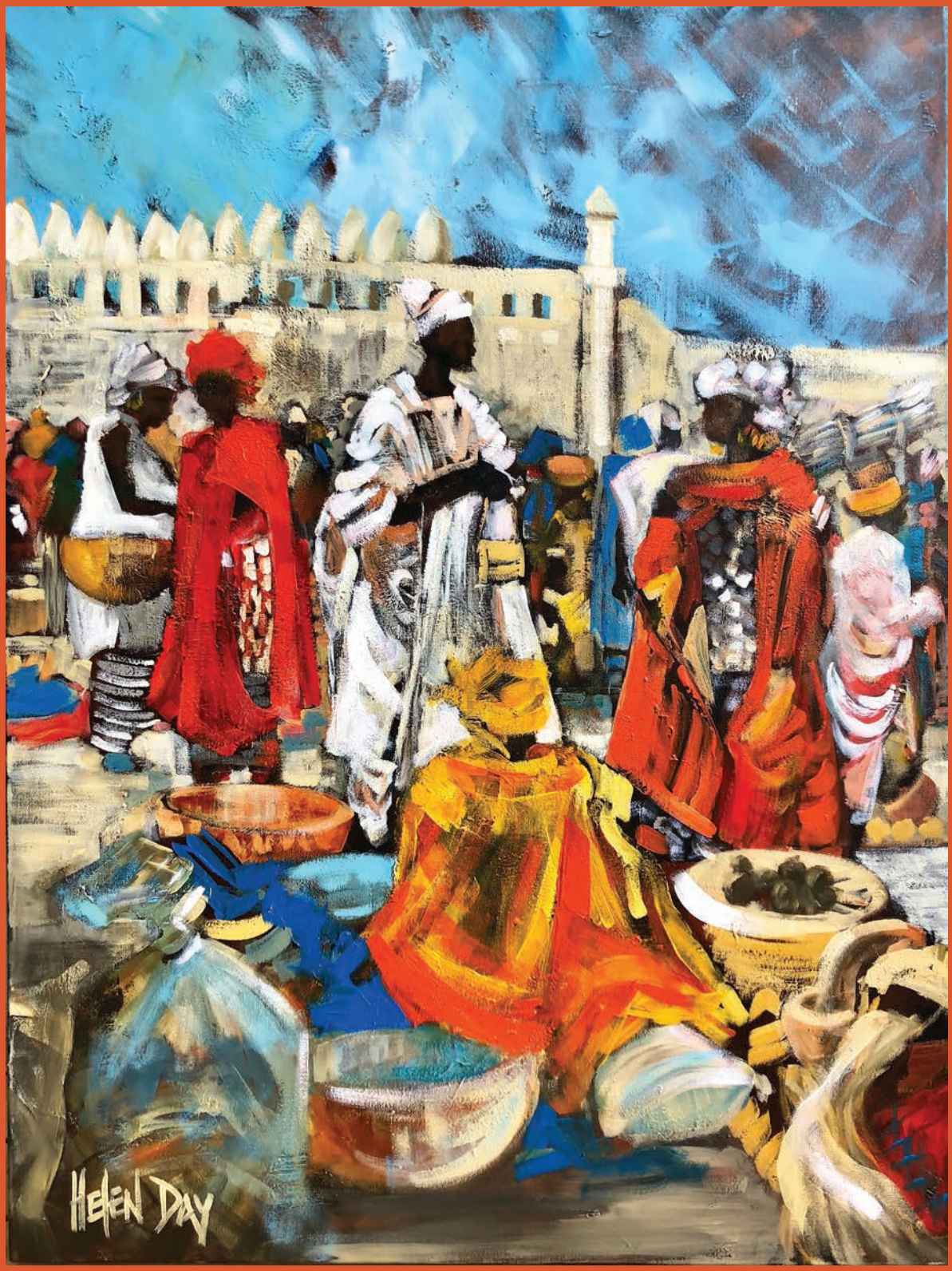
Critique of African Union and NEPAD's positions on gene drive mosquitoes for Malaria elimination



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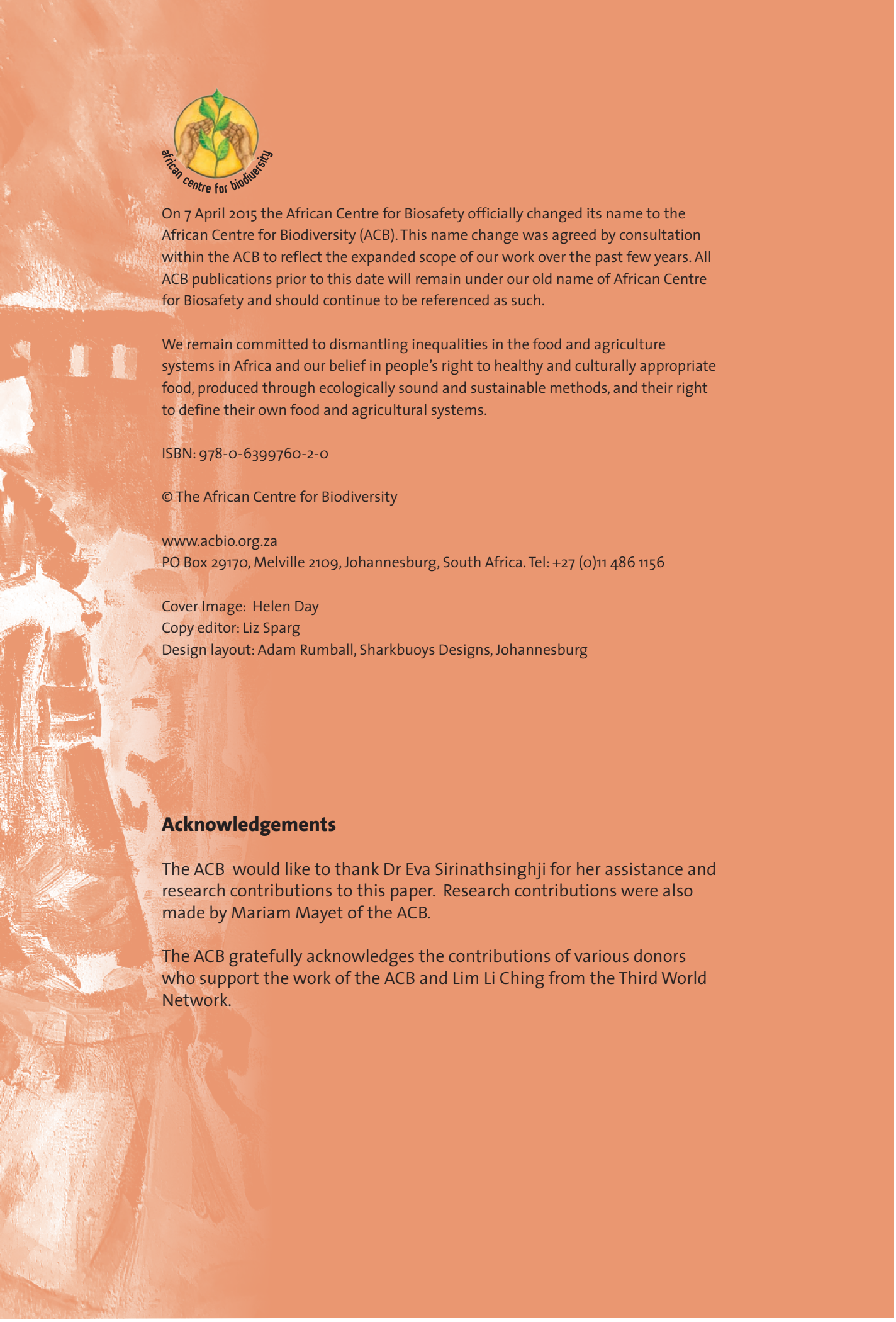

On 7 April 2015 the African Centre for Biosafety officially changed its name to the African Centre for Biodiversity (ACB). This name change was agreed by consultation within the ACB to reflect the expanded scope of our work over the past few years. All ACB publications prior to this date will remain under our old name of African Centre for Biosafety and should continue to be referenced as such.

We remain committed to dismantling inequalities in the food and agriculture systems in Africa and our belief in people's right to healthy and culturally appropriate food, produced through ecologically sound and sustainable methods, and their right to define their own food and agricultural systems.

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www.acbio.org.za
PO Box 29170, Melville 2109, Johannesburg, South Africa. Tel: +27 (0)11 486 1156

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Abbreviations

ABNE	African Biodiversity Network of Expertise
AHTEG	Ad Hoc Technical Expert Group (on Synthetic Biology)
AMRH	African Medicines Regulatory Harmonization
ANB	National Biosafety Agency (Agence Nationale de Biosécurité)
AU	African Union
CBD	Convention of Biological Diversity
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CSIRO	Commonwealth Scientific and Industrial Research Organisation
GM	Genetic modification
GMO	Genetically modified organism
DARPA	Defence Advanced Research Projects Agency
NEPAD	New Partnership for Africa's Development

About this paper

This paper presents a critique of the report published by the African Union's technical arm, New Partnership for Africa's Development (NEPAD) titled 'Gene Drives for Malaria Control and Elimination in Africa', published in June 2018 (NEPAD, 2018). The African Union (AU) report supports the potential use of mosquitoes carrying transgenic gene drive technologies for the control of malaria transmission across the AU member states.

Gene drive technologies are genetic modification (GM) strategies that will have the ability to spread through, and thus potentially alter, entire populations. Biosafety concerns include possible wider ecological, health, social and/or economic adverse impacts. These will spread across political/geographic borders and present critical challenges to national sovereignty and biosafety risk assessment that go beyond the current scope of regulations in place for standard GM techniques. Gene drive technologies also challenge fundamental social, cultural, ethical and political norms across communities and societies.

While there is an intense public relations drive by the Target Malaria project, a developer of gene drive technologies, to promote gene drive organisms, their deployment is fuelling intense policy, legal, cultural and ethical debates. It is expected that the technologies will take centre stage in the international negotiations of the Convention of Biological Diversity (CBD) in November 2018.

The AU report endorsing gene drive applied research and potential deployment for malaria eradication emerged in the absence of any agreed international governance standards for the release of the mosquitoes into the environment. It also emerged in the absence of a thorough understanding of how or even if such a technology will reduce malaria transmission – let alone eradicate it – across the AU's member states in the long term. Scientific data demonstrating or modeling efficacy efficacy of gene drive mosquito releases and how they would influence disease burden are still sorely lacking.

The infancy of the technology and the lack of underlying scientific evidence supporting it as a realistic malaria eradication tool raises serious ethical questions regarding the current hype and public relations drive pushing this risky techno-fix onto vast populations and ecosystems in Africa. Indeed, articles by gene drive researchers themselves state their awareness of how public perception could determine whether gene drives will eventually be released (Najjar et al., 2018). The proposal for the first gene drive application to be promoted as a public health solution for African children – instead of other applications, such as agriculture and conservation – appears to be a deliberate public relations strategy intended to direct the debate away from other planned uses that may not gain public support.

It is deeply concerning that the push for gene drives on the continent has already begun to take hold as it opens the door to the approval of the first GM animals ever to be released in Africa, in the form of GM, non-gene drive mosquitoes. The application to make open releases of GM mosquitoes was reportedly approved by the National Biosafety Agency (Agence Nationale de Biosécurité, ANB) in Burkina Faso in September 2018. Consequently, the first open release of GM mosquitoes in Africa is anticipated to occur at any time.[1,2] In the meanwhile, research is taking place that requires volunteers to expose themselves to wild-type mosquitos, thus also increasing risk of malaria exposure to themselves and others.

In part, the purpose of this GM mosquito experiment is to function as a 'trust experiment' to convince citizens who may be

1. 'A swarm of mutant mosquitoes is out to eradicate malaria.' Wired. 21 September 2018. https://www.wired.co.uk/article/mosquitos-crispr
2. Target Malaria welcomes the decision of the National Biosafety Agency of Burkina Faso to approve a small-scale release of genetically modified sterile male mosquitoes. Target Malaria. https://targetmalaria.org/wp-content/uploads/pdf/statement_authorisation_nba_bf.pdf

highly sceptical of the technology (TeleSur, 2018). There is no intention for this release to reduce malaria transmission.

This paper summarises the current state of gene drive research and critiques the unsubstantiated claims being made by gene drive developers and slavishly repeated in the African Union report. The purported benefits for malaria control are yet to be supported by concrete data, making a rush to develop enabling legislation to allow for applied research irresponsibly premature.

1. Introduction: What are gene drives?

Gene drives are an extreme form of GM that falls under the bracket of synthetic biology techniques, designed to alter the genetics of an entire population. To generate gene drive organisms, specific types of foreign (transgenic) genetic sequences are introduced into an organism, which are able to bias inheritance in such a way that the transgene is inherited at a higher rate than would occur under normal rules of inheritance. This defining (albeit still theoretical) ability to spread through an entire population introduces unprecedented challenges for containment of genetically modified organisms (GMOs). Any release, whether it emanates from a trial, deployment or accidental escape, may well be irreversible, presenting a vital distinction from first generation GMOs, where introduced transgenes would eventually be diluted out of the population, theoretically allowing for a degree of containment. Even the ability to contain first generation genetically modified crops has proven very difficult, with numerous escapes of unauthorised varieties following field trials, and the spread of transgenic constructs into conventional varieties and unauthorised regions (Price & Cotter, 2014).

Though the concept of gene drives has existed for decades, and a few rare examples of similar systems exist in nature, such as Medea selfish genes found in flour beetles, the development of new GM approaches, particularly the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 gene editing techniques, now offer a rapid and simple method to introduce synthetic gene drive systems to a wide variety of organisms. To date, gene drives have been introduced into yeast (DiCarlo et al., 2015), flies (Gantz & Bier, 2015), mosquitoes (Gantz et al., 2015; Hammond et al., 2016), and, this year (2018), mice (with only partial efficacy) (Grunwald et al., 2018) though none have been officially released into the environment.

In the context of malaria, Target Malaria and other research groups have developed two strategies. The first is to introduce gene drives into mosquitoes that will disrupt essential genes for survival, such as disrupting female fertility. This is designed to cause potential elimination of entire mosquito populations (population suppression). The second strategy is to use gene drives to alter the mosquito's ability to transmit malaria (population alteration), though this strategy has received less focus from developers, to date.

2. Target Malaria

The Target Malaria project, currently the largest research group working on gene drive technologies for malaria control, has been touted as the first potential application of gene drives in the world. Involving a consortium of research institutions led by Imperial College, London, it includes the CDC Foundation, USA; Fred Hutchinson Cancer Research Centre, USA; Institut de Recherche en Sciences de la Santé (IRSS), Burkina Faso; Keele University, UK; Malaria Research & Training Centre, Université des Sciences, des Techniques et des Technologies de Bamako, Mali; Polo d'Innovazione di Genomica, Genetica e Biologia (Polo GGB), Italy; USA; Uganda Virus Research Institute (UVRI), Uganda; University of Cambridge, UK; University of Notre Dame, USA; University of Oxford, UK; University of Perugia, Italy; and University of Washington, USA (Target Malaria, 2018).

The mosquitoes have been developed in laboratories based in the UK and the US, but part of the research project is also taking place in Burkina Faso, Mali and Uganda (according to Target Malaria's website they report to have also worked in Kenya)[3] to lay the regulatory, technical and institutional groundwork for eventual importation, research and release of mosquitoes in those countries.

Core funding for the project comes from the Bill and Melinda Gates Foundation, which has invested $75 million (Regalado, 2018), as well as the Open Philanthropy Project (founded by Facebook co-founder Dustin Moskovitz) who recently awarded $17.5 million to the project (Open Philanthropy Project). The Bill and Melinda Gates Foundation is one of the two main funders of gene drive research in general, the other being the US Military's Defence Advanced Research Projects Agency (DARPA) (Synbiowatch, 2017).

The Open Philanthropy Project also awarded NEPAD $2,350,000 to 'support the evaluation, preparation, and potential deployment of gene drive technologies in some African regions' in 2017, 'with the goal of supporting gene drive technologies to help eliminate malaria in Sub-Saharan Africa if feasible, ethical, safe, approved by the regulatory authorities, and supported by the affected communities'. This funding was awarded less than a year before this AU/NEPAD report supporting the potential deployment of gene drive mosquitoes across the African Union member states was published.

3. The AU report makes numerous unsubstantiated claims in support of gene drive development

The AU report makes several claims regarding the potential for gene drives to be a promising solution for malaria eradication. As expanded below, it is too early to make such claims, as substantiating scientific evidence is sorely lacking. The AU's claims go even beyond those currently made by certain gene drive developers themselves.

Claim 1: 'Gene drives present realistic options for effective disease control'

The development of synthetic CRISPR-based gene drive systems has been a very recent development, with the first laboratory demonstrations being published as recently as 2015 (Gantz and Bier, 2015). To date, proof of principle experiments has shown efficacy of gene drives in terms of their capacity to bias inheritance of the transgenic element over only a very limited number of generations in laboratory settings. However, even these first 'proof of principle' demonstrations in *A. gambiae* mosquitoes (Hammond et al., 2016) referenced by the AU report, still lack proof of functional efficacy, with a later follow-up study showing that resistance to the gene drive constructs developed in 80% of mosquitoes after only 25 generations (Hammond et al., 2017), with each generation being, on average, 1–2 weeks in the wild. Newer versions designed to reduce the likelihood of resistance have since been developed (Hammond et al., 2018; Kyrou et al., 2018), but only by reducing resistance development in the target sequences destined for gene drive modification (such as a gene essential for female fertility). We are yet to see if some sort of resistance will occur in these newer versions that have only recently been developed.

3. https://targetmalaria.org/where-we-operate/

While progress is being made to deal with resistance developing in the target sequences designed to be disrupted, resistance could also evolve towards the gene drive construct itself, such as within the nuclease 'cutting' enzyme, or the RNA guide sequence (the sequence designed to guide the gene drive construct to the target gene). Such a scenario has prompted a leading gene drive developer, Kevin Esvelt and his colleagues, in a recent publication to state:

> *...releasing a single gene drive system may not be enough, as it is likely that some form of resistance will evolve. This is unlikely to be caused by mutations that block cutting, which models predict, can be reliably overcome by targeting multiple sequences, but resistance arising from interference with the nuclease or the guide RNAs, their expression, or some unexpected avenue are all within the realm of possibility. (Najjar et al., 2018:p453)*

In the case of resistance, not only will gene drives fail to eliminate malaria, but such transgenic gene-drive resistant mosquitoes would still be present in the environment. As we have seen with other GM organisms, the process of genetic modification is an inherently unpredictable process that can have unintended additional effects on the genome, and thus on the whole organism. As such, even if they no longer harbour a functional gene drive system, such organisms would still have the potential to have adverse and yet unknown environmental and health effects.

As rightly stated in the AU report (AU, 2018), the technology is 'still in its infancy', requiring 'a series of validation and optimisation studies to be conducted rigorously in safe and secure laboratories'. However, the report nonetheless makes far-reaching claims that 'gene drives present *realistic options for effective disease control* [emphasis added]' and that 'potential benefits for African countries will almost *certainly be extensive* [emphasis added]' (AU, 2018: p2). The report goes on to endorse the passing of enabling legislation for gene drive development and eventual deployment, stating that 'regulators should facilitate and adapt essential guidelines and frameworks and where necessary, enact enabling legislation for the development and adjudication of the technology' and 'provide support for the conduct of laboratory, field and semi-field studies to verify the potential of the technology for various African settings' (AU, 2018: p2).

The report further states 'mathematical evaluations of both the population suppression and population alteration approaches to gene drives have demonstrated the potential to contribute to malaria elimination *within just a few years after initial* release [emphasis added]' (AU, 2018: p10). However, the evidence is totally inadequate to support such a claim. The main study the report relies on (Eckhoff et al, 2016) is a computer simulation. There are no observations to support the predictions of the model, nor are there baseline data such as the current dispersal patterns of the mosquito species that carry malaria. There is also no indication of how the model would be affected by climate change.

Even the best case scenario presented for Garki, where there is high seasonality that would affect the connectedness of mosquito populations and thus spread of gene drive mosquitoes, used a model that required weekly releases for a year, from 15 release points across a 10 x 10 km grid. Even then, in the case of a forest fire, the model predicted that wild-type mosquito populations would remain and repopulate the area to full recovery after gene drive releases are ceased.

Further, it assesses only two regions: Namawala, Tanzania, and Garki, Nigeria, and also models only one of the many malaria vectors, likely out of practical reasons for the study itself, making it difficult, if not impossible to extrapolate on how gene drives in multiple vectors would behave across the rest of the continent.

Even with their best case scenario presented by the Eckhoff model suggesting it might be possible to use gene drives to contribute to the elimination of malaria, whether this would actually work in the real world, how practicable it would be to carry it out, what it would cost, and to what extent other measures would also have to be employed remain unknown. The study's completely unjustified claim that 'Once the constructs

for each species have been developed, releasing these gene drive mosquitos for multiple species will succeed in eliminating malaria from this region', should be ignored by policy makers.

Above all, it impossible to be able to assess how accurately such models would reflect a real-life scenario.

Gene drive developers have also concluded about the Eckhoff (2017) study: 'Self-propagating gene drive systems are not a silver bullet, not least because the natural spread of these systems would be quite slow: models suggest that natural spread from a single release would require over a decade to affect a mid-sized African country' (P. Welkhoff, personal communication). Effective deployment will require a systematic plan for geographically distributed releases across the entire target area, in combination with bed nets, insecticide spraying, antimalarial treatment and other control measures' (Najjar et al., 2018).

The history of malaria eradication programs also presents us with wider questions regarding the validity of strategies focusing on vector elimination. As we have seen in Nigeria, a 1970s program to eradicate *A. gambiae* populations using synthetic pesticides was highly successful in its execution, resulting in more than a 90% reduction in population numbers. However, due to the high vectorial capacity of *A. gambiae*, and its extreme preference for human blood, this did not reduce the transmission of malaria (Molineaux & Gramiccia, 1980). As stated by Bill Gates himself in a recent interview, 'None of these [gene technology] constructs will actually wipe out the species ... It will evolve back. After all, evolutionary pressures always push back' (Kelland, 2018). This begs the question whether this strategy, even if effective in dramatically reducing mosquito numbers, will translate to malaria reduction, let alone eradication. The failure of previous eradication programs has also been attributed to the failure to also address underlying systemic economic, social, health and environmental issues. As such, though the technical developments of gene drives may be novel, the concept of vector eradication is not.

We must carefully address the question of whether this latest vector elimination techno-fix will improve on these previous attempts. Indeed, historical assessment of the Malaria Eradication Program conducted in the 1950s to 1960s, which focused on the use of synthetic pesticides, shows that the program was successful primarily only in three types of region (Packard, 2007). The first was in island nations, where it was easier to control transmission and reintroduction, such as Caribbean nations. The second comprised of Eastern European nations, which were successful despite being deprived economically, as they were still able to rely on prior developed healthcare systems to support long-term eradication efforts. The last group of nations that successfully benefited from the program were economically well-off nations, such as the USA and Spain, where larger amounts of resources could be dedicated to eradication efforts, and where people were better able to protect themselves with bed nets, screens, adequate housing, sanitation and other such personal and public efforts. Other examples include smaller regions, such as Veracruz in Mexico, and Kerala in India, which successfully benefitted from the program due to prior implementation of sanitary engineering projects, improved public services in the case of Veracruz, and prior developments and investments in health care and education programs in the case of Kerala. Unfortunately, Kerala was not able to sustain this success, due to the lack of eradication in other parts of India. As appears to be the case with gene drives now, the common faith underlying the eradication program was that Western science and technology could transform poorer countries. However, the program was a failure in sub-Saharan Africa and many other poorer regions of the world.

In summary, there remains a lack of data necessary for predicting potential efficacy of gene drive technology. Such data should have been thoroughly collated and independently critiqued prior to the well-resourced and misplaced PR drive already underway to quell public unease and persuade governments and international regulatory bodies to enable legislation for their environmental release, including claims that 'millions of lives could be saved' (Matthews, 2018), and that gene drives could be a 'game changer'

(Opoku Gakpo, 2018). Fundamental questions also remain about the narrow focus on technologies, while the underlying societal causes of malaria transmission are ignored.

Claim 2: 'No major risks are foreseen that cannot be mitigated'

With regards to potential ecological risks, the AU report is dismissive of the potential impact of suppressing, or potentially eliminating *A. gambiae* populations. It states that *A. gambiae* is not a 'keystone' species in the environment. While not completely inaccurate, this nonetheless could be considered a misleading statement, when, as mentioned previously, *A. gambiae* is not the only species likely to be targeted with gene drive technologies. Currently, the evidence to dismiss the impact of wiping out additional malaria vectors remains lacking, such as *A. funestus*, which the AU report describes as a species that remains 'elusive and particularly challenging to study' (AU: p12). Indeed, Target Malaria is yet to embark on planned projects to understand how fish, bats, flowers and insects would respond to such a scenario (Zhang, 2018), despite repeated claims circulating in the media and gene drive journal publications that any negative effects are unlikely. As other gene drive developers have acknowledged: 'Our knowledge of ecosystem-level species interactions is limited. Even when we know how to edit the genome to achieve the desired outcome, predicting its effects on other species is difficult' (Min et al., 2018). Esvelt and Gemmell (2017) have also highlighted the potential for gene drive organisms to become an invasive species: 'The bottom line is that making a standard, self-propagating CRISPR-based gene drive system is likely equivalent to creating a new, highly invasive species'. They further state: 'Both will likely spread to any ecosystem in which they are viable, possibly causing ecological change'.

Gene drives also present a unique challenge for assessing risk, as it is not possible to assess potential impacts on 'receiving environments' prior to release. How can gene drives be assessed before deployment if one cannot adequately test them without deploying them? Current risk assessment methods are, thus, unfit for assessing gene drives, and, furthermore, the data currently does not exist to fully assess risk (Simon et al., 2018). It is particularly difficult to assess how they would behave across time and space, considering the potential accumulation of mutations that may occur due to off-target activity of CRISPR systems at each generation, also dependant on the genetic diversity of the populations it targets.

How such evolutionary changes occur in the context of climate change further complicates any predictions of lack of risk at various levels. At the level of the organism, would it become toxic as a food source, for example? How would behavioural interactions change? Would there be evolving shifts in the balance of the ecosystem? Would it result in niche replacement? Would the gene drive system spread to other mosquito species? The latest version of gene drives (Kyrou et al., 2018) targets a genetic sequence that is highly conserved between all sixteen Anopheles mosquito species, such that spread of the gene drives to any of these species could also induce their population suppression (GMWatch, 2018). This also undermines the idea that the gene drives are highly specific in comparison to synthetic pesticides in terms of harm to non-target organisms.

In terms of health impacts, the above-mentioned potential outcomes could have serious implications. How would for example, the scenario of niche replacement affect transmission of malaria or other vector-borne diseases? This was only touched upon in a single sentence in the AU report, but the paper claims that 'no major risk factors are foreseen that cannot be mitigated, and the potential benefits associated with malaria elimination will almost certainly outweigh any minor risks observed' (AU: p23). However, critical questions remain about potential negative effects, even on malaria transmission itself. What if, for example, gene drives were successful in reducing population numbers but unable to eradicate them completely, as predicted by some, including Bill Gates? In this scenario, past experiences show that, when numbers eventually recover, failures to sustain high levels of malaria protection could have serious health consequences for populations left unprotected, especially in holoendemic regions, where repeated exposure has led to

functional acquired immunity to disease. This form of immunity is not permanent and can thus be undermined by loss or interruption of exposure. Such a scenario occurred in Madagascar, where control measures broke down in the 1970s, leading to disastrous consequences a few years later, as a result of disease resurgence amongst a vulnerable population and tens of thousands of deaths in only a few months (see Packard, 2007). Such a 'rebound effect' may even lead to greater disease burden (Scott et al., 2002; Azra et al., 2009). Such problems have long been an important area of concern amongst malariologists. The issue of the 'rebound effect' raises difficult questions that appear to be absent from the gene drive discussions, which, disturbingly, only focus on the best-case scenario of malaria eradication, while discussion of potential risk has been limited to environmental effects.

Claim 3. 'Development of the gene drive technology should follow a stepwise approach'

The AU report (NEPAD, 2018) advocates for a phased testing approach to gene drive mosquitoes that moves in a step-wise manner from laboratory studies, to 'confined' small-scale field testing in island locations, for example, followed by open small-scale field releases, ending with large-scale field releases.

The 'confined' small-scale release is designed to assess 'stability, genetic flow, various entomological outcomes, possible implementation strategies and likelihood of development of adverse mutations that could prevent the spread of the drive'. The small-scale field releases are to test for 'field efficacy and stability, genetic flow, acceptance by human communities in target areas, reproductive fitness of the mosquitoes, various entomological outcomes, potential implementation strategies and also the likelihood of resistance to the drives'. Large-scale 'controlled' field releases are to assess impact of the intervention on clinical parameters of disease.

While advocating a phased approach to assess 'safety and efficacy', there is also acknowledgement in the AU report that such a phased approach will 'likely overlap', such that the gene drive mosquitoes released under confined small-scale trials may 'spread beyond the initial areas of release and would effectively transform into a large-scale release'. This statement acknowledges the fallacy of the idea of phased testing and the ability for environmental containment in the event of a 'confined' field trial. Further, as stated by the Convention for Biological Diversity's Ad Hoc Technical Expert Group on Synthetic Biology: 'Islands are not ecologically fully contained environments and should not be regarded as fulfilling the conditions in the definition of contained use as per Article 3 of the Cartagena Protocol unless it is so demonstrated' (AHTEG, 2017: Para 51 (b)) – i.e. islands or 'confined' field trials are essentially releases into the environment. Assessing genetic flow and acceptance from communities during a trial that, in reality, is an uncontrolled environmental release goes against the principle of precaution and also the legal obligation to obtain full free, prior and informed consent to affected communities. As gene drive developers have iterated: 'It is doubtful whether field trials of the self-propagating drive system can be conducted without a substantial risk of unintended spread.' (Najjar et al., 2018). This brings us back to the above-mentioned issue of not being able to assess the risk of deploying gene drives without first deploying them.

It is also interesting to note that, while researchers such as Esvelt have recently received funding from DARPA under the 'Safe Genes Program' to develop localised gene drive systems that are designed to have limited spread, it is 'global' gene drives that are being recommended for malaria eradication. The rationale for this is that malaria is an urgent issue, and as such, potential benefits outweigh any perceived risk. Further, it seems that entire mosquito populations would need to be eradicated or dramatically suppressed to witness a reduction in disease burden.

The principle of localised systems, though currently largely theoretical and not yet empirically tested, is to limit their spread in a spatial or temporal manner, to prevent modifying or eliminating an entire population. Localised systems have been touted as a potentially safer way to test

gene drive systems prior to the deployment of global drives. However, in the case of the malaria in Africa, such safeguards, even if they are largely theoretical and insufficient to protect against the risks, seem to have been put aside.

4. Unsubstantiated hype surrounding gene drives opens up the continent to GM insects

Even if there are no eventual gene drive releases, the premature misguided hype surrounding gene drives for malaria eradication, and the political sanctioning now by the AU, are already opening the doors to other forms of genetically modified mosquitoes. Burkina Faso has just approved the release of GM mosquitoes, called Ac(DSM)2, in the first phase of a three-phased strategy that will ultimately result in the release of gene drive versions in the final phase. Ac(DSM)2 mosquitoes are designed to be sterile, in order to reduce mosquito numbers, but do not carry gene drive constructs. This trial, expected to be taking place in the very near future, will be the first ever release of a GM animal anywhere on the African continent.

The goal of this first phase is not designed to reduce mosquito numbers or have a 'direct benefit' but instead, 'the purpose is for the African team who lead the project to carefully learn how to care for, release, and collect mosquitos', and to 'generate data on the daily survival rate of released Ac(DSM)2 males and to assess their movement from a defined release point'(letter to TWN and GeneWatch UK, from Ethics Advisory Committee to Target Malaria, 2018). The risk assessment conducted for Target Malaria by the Australian federal government agency Commonwealth Scientific and Industrial Research Organisation (CSIRO), also states that data generated from the field release will 'further inform an understanding of how outcomes from indoor contained use experiments can be extrapolated to a field entomology context.' (CSIRO, 2018). However, scientists involved in the project have also described it as a 'trust experiment',[4] while Esvelt and colleagues claim the purpose is to 'assess the ecological effects of suppressing mosquito populations and *build confidence in local capabilities without the risk posed by a self-propagating gene drive*, [emphasis added]' (Najjar et al., 2018). Such statements raise the question as to whether the release of these sterile GM mosquitoes, which share limited behavioural dynamics with future gene drive systems, is more about quelling public unease than anything else.

Numerous legal and regulatory concerns surround the release of the GM mosquitoes in Burkina Faso (see ACB, TWN & GeneWatch UK, 2017; ACB, TWN & GeneWatch UK, 2018). Biosafety concerns are also raised by the experiment. For example, the trial is supposed to release only male mosquitoes, which do not bite humans. The risk assessment conducted however, predicts that 5 out of every 1 000 mosquitoes released will be females. Further, as seen with another trial testing a different genetically modified strain in the Cayman Islands, higher than predicted females were released (ACB, TWN & GeneWatch UK, 2018). This opens up the possibility of persistence of the GM trait in the environment, and human exposure to bites from GM mosquitoes. The risk assessment published by CSIRO (2018:p22) also states that 'A key challenge to probabilistic risk assessment for a novel technology is the lack of empirical information on its safety and reliability'. Further, the assessment revealed large disagreements between the experts involved, as to whether various risks were probable or not. While additional experiments were suggested by the experts, these do not appear to have been published for independent analysis, or, indeed, by the community to be exposed to the trial.

Once the 'enabling' and 'harmonised' legislation described in the AU report is put in place, it will lay the groundwork for yet more GM organisms to enter at an accelerated pace across the continent. The report makes general remarks, for example, that the issue

4. GMWatch. 2018. Gene drives breakthrough needs urgent restraint. https://www.gmwatch.org/en/news/latest-news/18474 [accessed 30 September 2018]

of transboundary movement 'presumably calls for coordination among neighbouring countries' and that the cross-sector aspect of gene drives means that:

> *'the regulatory process needs to consider multiple aspects, ranging from technologies initiated by agricultural genetic modification processes, through transgenic insect vector control, to health value propositions. This will require bridging from agriculture to health and the regulatory pathway being targeted will form a break- through model for other emerging technologies that need to be harnessed for economic development in future. (AU, 2018:p25).*

As such, NEPAD should play an 'enabling' role by coordinating processes across various levels, including the African Biosafety Network of Expertise (ABNE) program, and the African Medicines Regulatory Harmonization (AMRH) program.

5. Questionable ethical practices involving human subjects in Burkina Faso

Serious ethical questions surround the Target Malaria project, including the conduct of the current research underway in Burkina Faso. The consent form to be signed by volunteers asks local people to expose themselves to mosquito bites nightly for four nights per week once a month over the course of 12 months, in exchange for a financial reward. This project thus provides a heavy incentive for people to expose themselves to wild-type mosquitoes carrying malaria and other vector borne diseases, putting themselves and others around them at risk. It appears to allow even those who have tested positive for malaria prior to the trial but who do not display symptoms to participate, stating: 'If you are in good enough health (even in cases of positive diagnosis but you are not showing any signs or symptoms of malaria) and that you confirm your intention to participate in the activity, you will be placed in an inside room, or outside, as decided by the team. You will be seated on a support [bed?] with the lower part of your leg exposed up to the knee, so that the mosquitos land on it.' Participants are then required to vacuum up mosquitoes, to collect them for analysis. Any mosquito that bites someone who has malaria and is not collected, therefore has the potential to bite someone else in the community, increasing the risk of exposing non-participants to malaria. The form acknowledges the risk of contracting malaria, stating: 'It is possible to get bitten by a mosquito and to be infected by malaria or another sickness transmitted by the vector (mosquito) during the collection.'

Though the form declares that anyone who shows signs of malaria will be treated, and costs covered by the project, there is no indication that supplies of such treatments and practitioners will be ensured prior to the experiment, neither is there any offer of private healthcare coverage. Further, the form does not specify if costs would be covered in the event of contracting another vector-borne disease, which also does not appear to be part of the monitoring effort.

Increasing the risk of exposure to a serious disease, in order to 'have a better idea of the behaviour of mosquitos' that 'could in the future be of help to the community and the country in efforts to better control mosquitos and malaria' is, clearly, highly unethical. It is unfortunately reminiscent of past racialised and neo-colonial practices, such as the infamous Tuskegee and Guatemalan experiments performed by US researchers on African American and Guatemalan people, respectively. The researchers were working on syphilis and other sexually transmitted diseases, following concern over the adverse impact such diseases were having on the US military during World War II. While the goal was to understand the effect they had on the body, and to test whether existing treatments were effective, the abhorrent practices included exploiting disempowered people by infecting them with disease, while not providing treatment. Though a certain level of treatment is being offered in this case, it nevertheless increases the risk of illness in the first place.

The Bill and Melinda Gates Foundation has

also sponsored dubious medical practices in the past. The UK's *Independent* newspaper investigated the widespread practice of pharmaceutical trial outsourcing to India, and found that one such Gate's-sponsored vaccination trial involved the recruitment of hundreds of girls for an immunisation study, without parental consent (consent was given only by the government hostel), and resulted in the death of several girls (Buncombe & Lakhani, 2011). The trial was later halted by the federal authorities. The practice of outsourcing trials has hugely reduced research costs for pharmaceutical companies.

Further, an article promoted by Target Malaria employees on social media indicates that the sterile GM mosquitoes are 'regular', which is misleading considering this is the first release of this particular GM mosquito anywhere in the world. It also claims in a STAT report that there has yet to be any discussion with the residents of the intention to release gene drive versions in the future because Target Malaria don't want to give false hope for a technology that is not yet ready, and also because gene drives are hard to understand: 'even in Europe and in North America, it's complex to understand gene drives in one shot' (Swetlitz, 2017). Target Malaria's ethics set a dangerous tone for what is to come once the technologies have been deemed fit for release. Indeed, one gene drive developer, Ethan Bier, was recently quoted in *Vox* as saying that gene drives are very close to being ready and that, while 'we *shouldn't* release anything without regulatory approval and much more consideration ... To be honest with you, if there were some kind of emergency and one absolutely needed to do it, we could pretty much do it' (Matthews, 2018).

Taken together, such activities suggest that the Target Malaria project is treating people as human guinea-pigs. There is questionable informed consent when financial incentives are being used to increase exposure to mosquitoes. Crucially, no published environmental risk assessment other than the one by Target Malaria itself has been published, and there have been no independent public engagement activities (ACB & GeneWatch UK, 2018). The question must be asked whether the AU has consulted civil society, as well as other important stakeholders from various sectors, including those involved in public health.

Gene drives are being targeted for Africa before anywhere else in the world. Despite this being a 'philanthropic' venture to combat a public health issue, profits from future gene drive applications may well come off the backs of human experiments that first risked the health of the people of Burkina Faso.

We ask the AU if they have taken on board the ethical implications of sanctioning such kinds of research that puts the health of its citizens at risk. If they have not, we urge the AU to do so before moving forward further with Target Malaria or other gene drive technologies.

6. Conclusions

Malaria eradication is a major health concern and it is understandable that nations seek novel methods to eradicate it. In efforts to rush in enabling legislation for its deployment, there has been an absence in the gene drive debate on wider issues that affect malaria transmission and disease burden. Further, the field of gene drive research and development is currently in its infancy. The purported claims that such technologies are the next saviour for malaria eradication therefore remain unfounded. If developers are ultimately successful in generating gene drives that can suppress vector populations, their ability to eradicate malaria remains questionable unless they are successful in completely wiping out all vector species, which then leads us to the biosafety uncertainties and risks of inflicting such an extreme ecological effect across an entire region.

As part of a network of over 170 international civil society organisations, the ACB called for a moratorium on gene drive releases in 2016, including applied research such as open field trial releases, until further understanding of the potential risks are thoroughly understood (ETC group, 2016). It is vital that serious governance gaps are urgently addressed. Concerns also remain regarding the inability

to regulate transboundary movement; the ability to contain gene drive organisms following both field trial and commercial releases; issues surrounding monitoring, assessment and liability; and free, prior and informed consent, particularly with regards to lands and territories of indigenous and local communities as enshrined in the UN Declaration on the Rights of Indigenous Peoples.

We therefore urge the governments of the African Union member states to support such a halt in gene drive releases that may have unforeseen and irreversible effects across the continent.

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